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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/330,909	06/11/99	WOLFF J	MIRUS.011.01

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EXAMINER	
WOITACH,J	
ART UNIT	**PAPER NUMBER**
1632	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary

Application No.	Applicant(s)
09/330,909	Wolf et al.
Examiner	**Group Art Unit**
Joseph Woitach	1632

☒ Responsive to communication(s) filed on *Dec 12, 2000*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-20* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6,7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicants petition to revive application 09/330,909 has been granted, paper number 11.

Applicants amendment filed December 12, 2000, paper number 10, has been received and entered. Claims 1, 3, 5-8 and 10-18 have been amended. Claims 1-20 are pending and currently under examination.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The specification must be amended so that the specific reference to the prior application is in the form of a sentence (37 CFR 1.78) .

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-20 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue that the specification provides guidance and enablement for reporter genes. Further, applicants argue that all polynucleotides are structurally identical and thus would not produce different nor negative effects on delivery and expression of other transgenes. Finally, Applicants argue that the level of expression of a given gene can be regulated by the choice of promoter and that the expression of a transgene can be modified depending on the application. Applicants arguments have been fully considered but not found persuasive.

The specification provides guidance on the use of two commercially available reporter DNA plasmid constructs. The specification does not give specific guidance regarding the use of other genes nor other promoter sequences, nor which specific gene and specific promoter should combined to be used to treat any disease. As noted in the previous office action, the physiological art in general is acknowledged to be unpredictable at the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. As pointed out by Verma *et al.* "there is still no single outcome that we can point to as a success story" and that, "the problem has been an inability to deliver genes efficiently and to obtain sustained expression." Further, Anderson states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease." Examiner agrees in part with Applicant that the delivery of a nucleic acid is not limited structurally, however Applicants have not pointed to the specification providing the needed guidance that serves as a

nexus between the art recognized obstacles of gene therapy and Applicants arguments that expression can be modified depending on the needed application. Applicants have described a method to introduce and express two commercially available plasmid DNA vectors, but essentially all of the work required to ultimately develop the use of specific genes under the correct regulation of a proper promoter construct that results in a therapeutic effect has been left for others.

Therefore, for the reasons discussed above and of record, in view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 1 is vague and unclear because injection/administration of the nucleic acid can be made into any blood vessel however, the delivery of the nucleic acid is to a specific tissue or cell, in this case a heart tissue and heart muscle cell. The claim is unclear on how administration of the

nucleic acid in any blood vessel is specifically targeted to a heart muscle cell. Further, 'the heart muscle cell' does not have antecedent basis.

Claim 6, 11, 14, 17 are vague, unclear and indefinite because it is not clear if the nucleic acid contained in the virus is the viral genome or other nucleic acids which is not usually inserted into the viral capsid, for example an artificially created capsid containing a plasmid.

Claim 7 is vague and indefinite in its recitation of "nucleic acid modifies expression in a cell" because it is unclear what modifications are expected and how the modifications are brought about. It is unclear to what specific structure Applicant refers, while a cell is a definite structure what expression and how (up or down) it is modified is unclear.

Claim 18 is incomplete because no process steps are present where "therapy" occurs. The method ends with the production of a therapeutic protein, however it is unclear what is therapeutic effect. Further, since expression of therapeutic protein can occur anywhere there is no clear connection between the location and expression of the nucleic acid and the resulting therapy.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 1-17 rejected under 35 U.S.C. 102(a) as being clearly anticipated by Leclerc *et al.* is withdrawn.

Leclerc *et al.* teach the delivery and expression of a transgene in an artery. Applicants amendment to recite delivery of a nucleic acid to a heart muscle cell has obviated the basis of this rejection.

Claims 1-17 stand rejected under 35 U.S.C. 102(a) as being clearly anticipated by Mann *et al.* (US patent # 5,922,687), Isner *et al.* (US patent # 5,830,879) and Hajjar *et al.*

Applicants argue that the amendment of claim 1 to recite 'heart muscle cell' instead of 'cardiac tissue' has obviated the basis of rejection for Isner *et al.* (US patent # 5,830,879) and Hajjar *et al.* who only teach delivery to endothelial cells. Further, Applicants argue that Mann *et al.* (US patent # 5,922,687) does not anticipate the claimed invention because the present invention does not require a 'sealed enclosure' as taught by Mann *et al.* Applicants arguments have been fully considered but not found persuasive.

Both Isner *et al.* and Hajjar *et al.* teach the delivery of a nucleic acid to the heart. As pointed out in the previous office action Isner *et al.* deliver vectors by use of a catheter directly to a specified area and Hajjar *et al.* uses an adenoviral vector for delivery and expression, and in

both circumstances expression of the administered gene is detected in the heart (Isner *et al.* Figure 12 and Hajjar *et al.* Figure 1). Further, Hajjar *et al.* specifically report expression throughout the myocardium in particular in '30% of the myocytes in the distribution of the coronary artery' (page 5254-5; bridging paragraph). Each of these references provide the necessary guidance and examples demonstrating the delivery and expression of a nucleic acid to a heart muscle cell and thus, anticipates the claimed invention.

Examiner agrees that Mann *et al.* does teach to use a 'sealed enclosure' for the delivery of a nucleic acid into the heart by establishing an incubation pressure which facilitates the uptake of nucleic acid by the cell. However, the claimed method is not limited to any specific means of introducing a nucleic acid into a blood vessel or delivering the nucleic acid to a heart muscle cell. Further, Mann *et al.* do teach alternative means not requiring a sealed apparatus, for example the method using a catheter for delivery (Figure 4) which is similar to that taught by Isner *et al.* In the example which uses a catheter the increase in pressure is created by increasing the liquid volume between a double balloon catheter. Therefore, because the process disclosed by Mann *et al.* includes all the method steps recited in the claims it anticipates the claimed invention.

Therefore, for the reasons above and of record the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mann *et al.* (US patent # 5,922,687) in view of Morishita *et al.*

Applicants argue that Mann *et al.* explicitly requires a sealed enclosure for delivery of the nucleic acid. Further, Morishita *et al.* disclose *in vitro* methods of transfection and that one of ordinary skill in the art would not combine the two references to obtain an *in vivo* method. Applicants arguments have been fully considered but not found persuasive.

Examiner agrees that Mann *et al.* teach the use of a sealed apparatus, however as pointed out in the previous office action, Mann *et al.* also teach a method of intracellular delivery of nucleic acid via a catheter. Mann *et al.* teach to use a catheter to isolate the area for delivery and use pressure to increase the uptake of the naked nucleic acid. However, Mann *et al.* only suggest the use of a nucleic acid attached to other molecules such as liposomes, HVJ liposomes viral vectors, viruses (column 3; lines 15-24) but do not teach the specific methodology using these molecules to increase the uptake of the nucleic acid. Morishita *et al.* is introduced as a secondary

reference to teach what was generally known for gene delivery and to demonstrate an expectation of success in the uptake and expression of DNA as; naked DNA, liposome complexes and HVJ/liposome complexes into a cell. Mann *et al.* suggest the use of methods and compounds to increase the uptake of a nucleic acid as used in Morishita *et al.* Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the methods of Morishita *et al.* to increase the efficiency and expression of delivery of a nucleic acid to cardiac tissue as described by Mann *et al.*Thus, for the reasons above and of record the claimed invention as a whole was clearly *prima facie* obvious and therefore the rejection is maintained.

Conclusion

No claim is allowed.

Applicants amendments to the claims have necessitated a new grounds of rejection, therefore **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608. The fax number for group 1600 is (703)308-4724.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pickney whose telephone number is (703) 305-3553.

Joseph T. Woitach

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